

CLINICAL RESEARCH

Beta-Blockers and Outcome in Heart Failure and Atrial Fibrillation

A Meta-Analysis

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- Objectives** The purpose of this study was to analyze the effect of beta blockade on outcome in patients with heart failure (HF) and atrial fibrillation (AF).
- Background** Beta-blockers are widely used in patients with HF and AF. Recommendation in current HF guidelines, however, is based on populations in which the most patients had sinus rhythm. Whether beta-blockers are as useful in AF is uncertain.
- Methods** Studies were included that investigated the effect of placebo-controlled, randomized beta-blocker therapy in patients with AF at baseline and HF with reduced systolic left ventricular ejection fraction (LVEF) <40%.
- Results** We identified 4 studies, which enrolled 8,680 patients with HF, and 1,677 of them had AF (19%; mean 68 years of age; 30% women); there were 842 patients treated with beta-blocker, and 835 with placebo. In AF patients, beta-blockade did not reduce mortality (odds ratio [OR]: 0.86 [95% confidence interval (CI): 0.66 to 1.13]; $p = 0.28$), while in sinus rhythm patients, there was a significant reduction (OR: 0.63 [95% CI: 0.54 to 0.73]; $p < 0.0001$). Interaction analysis showed significant interaction of the effects of beta-blocker therapy in AF versus that in sinus rhythm ($p = 0.048$). By meta-regression analysis, we did not find confounding by all relevant covariates. Beta-blocker therapy was not associated with a reduction in HF hospitalizations in AF (OR: 1.11 [95% CI: 0.85 to 1.47]; $p = 0.44$), in contrast to sinus rhythm (OR: 0.58 [95% CI: 0.49 to 0.68]; $p < 0.0001$). There was a significant interaction of the effects of beta-blocker therapy in AF versus that in sinus rhythm ($p < 0.001$).
- Conclusions** Our findings suggest that the effect of beta-blockers on outcome in HF patients with reduced systolic LVEF who have AF is less than in those who have sinus rhythm. (J Am Coll Cardiol HF 2013;1:21–8) © 2013 by the American College of Cardiology Foundation

Beta-blockers are a cornerstone treatment of patients with heart failure (HF) (1). Randomized trials with carvedilol (U.S. Carvedilol Study [2] and COPENICUS [Carvedilol Prospective Randomized Cumulative Survival] [3,4]), metoprolol (MERIT-HF [Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure] [5]), bisoprolol (CIBIS-II [Cardiac Insufficiency Bisoprolol Study II] [6]), and nebivolol (SENIORS [Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization

in Seniors With Heart Failure] [7]) showed that beta-blockers reduce morbidity and mortality in HF patients. As a result, these agents have received a Class IA recommendation in current HF guidelines (1). Atrial fibrillation (AF) is common in HF and occurs in 30% to 40% of all patients (8). The HF trials that led to the recommendations also included a proportion of patients with AF. In current guidelines for HF therapy (1), the recommendation for beta-blockers is not

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restricted to patients with sinus rhythm and includes all HF patients (i.e., also for those with AF) but it is unknown whether beta-blockers are as effective in those patients as they are in patients with sinus rhythm.

In patients with sinus rhythm with and without HF, lower heart rate is associated with a better outcome (9–11) and reduction of heart rate (by beta-blockers) probably plays an important role in the beneficial effect of these drugs.

**Abbreviations
and Acronyms****AF** = atrial fibrillation**CI** = confidence interval**HF** = heart failure**LVEF** = left ventricular
ejection fraction**NYHA** = New York Heart
Association**OR** = odds ratio

In patients with AF, with or without HF, lower heart rate, however, is not associated with a better outcome as was shown recently (12).

Although patients with AF were included in the large HF trials, the absolute number of patients with AF in each individual study was limited (13–16). The aim of the present meta-analysis therefore was to assess the effect

of beta-blockade on outcome (i.e., mortality and hospitalization for HF) in patients with both HF and AF.

Methods

Literature search. We searched MEDLINE using search tools provided by PubMed and OVID. These search tools have been validated by Haynes *et al.* (17) to optimize retrieval. We used the keywords atrial fibrillation, heart failure, beta-blocker therapy, beta-blockade, and medical therapy and a combination of these terms and included papers published in English. Furthermore, we reviewed reference lists from eligible studies, used the “see related articles” feature for key publications in PubMed, consulted the Cochrane Library, and searched the ISI Web of Knowledge for publications that cited key publications.

Study selection. Studies were included that investigated the effect of placebo-controlled, randomized beta-blocker therapy in patients with AF documented by electrocardiography (ECG) at baseline and HF with reduced systolic left ventricular ejection fraction (LVEF) <40%. We restricted our final search to beta-blockers that are registered for HF treatment (i.e., metoprolol, carvedilol, bisoprolol, nebivolol). For this reason, one large outcome trial which examined bucindolol (BEST [Beta-Blocker Evaluation of Survival Trial]) was not included (18). One study (SENIORS [Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure]) included both patients with reduced and preserved LVEF. For the present analysis, we included only patients with LVEF <35%, because this was the cutoff value used in that study, both in the methodology in the main study (7) and in the separate publications of the 2 groups (19). After study selection, we extracted data for the sinus rhythm group for comparison with those for AF patients.

Articles were excluded if: 1) no data were available for clinical outcomes; 2) data were published only in abstract form; 3) no definition for HF was given, either by combination of symptoms and signs (using New York Heart Association [NYHA] functional class or physical examination), imaging (impaired LVEF), or a combination of both; and 4) no distinction was made between AF and sinus rhythm. The primary outcome measure was defined as all-cause mortality. The secondary outcome variable was hospital admission for

worsening HF. For each study, we evaluated the effect of beta-blocker treatment on both of these outcomes, separately, in patients with AF and in those in sinus rhythm included.

Quality of studies in analysis. The quality of the individual studies was assessed by 11 factors: 1) sufficiently specified inclusion and exclusion criteria; 2) sufficient explanation of sample selection; 3) specification of clinical and demographic variables; 4) representation of the study sample for the mentioned patient population; 5) specification of outcome measures; 6) definition of AF; 7) assessment of the dose-response relationship between beta-blocker therapy and outcome; 8) adjustment for possible confounders in the analysis; 9) reporting of rates of patients lost to follow-up; 10) study design; and 11) duration of follow-up. Grading was as follows: good quality included 8 to 11 criteria, fair quality included 5 to 7 criteria, and poor quality included <5 criteria (20).

Statistical analysis. Meta-analysis was performed using a fixed-effects model to determine risk associated with beta-blocker therapy and all-cause mortality as measured by combined crude mortality rates. In secondary analysis, hospital admission for HF was studied in a similar manner. For comparison with patients in sinus rhythm, subgroup analysis was carried out by testing of heterogeneity across subgroups and by testing the null-hypothesis that the proportion of total variation in subgroup estimates was due to genuine variation across subgroups, rather than sampling error. Second, we carried out interaction analysis between subgroups of patients with AF and sinus rhythm, based on methods described by Altman and Bland (21). Among studies, heterogeneity of risk estimates was examined using a standard chi-square test and I^2 statistic for heterogeneity. Reasons for diversity in study results were explored using metaregression analysis. Variables explored included age, sex, baseline rhythm, hypertension, diabetes, ischemic heart disease, NYHA functional class, LVEF, heart rate, heart rate reduction, blood pressure, and medical treatments, including use of diuresis and digitalis and renin angiotensin system inhibitor. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and p values. Evidence of publication bias was assessed by visual inspection of the funnel plot. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata version 11.0 software (Stata, College Station, Texas) and RevMan version 5.1 software (22).

Results

Study search and general characteristics. The search retrieved 248 citations, 4 of which fulfilled all criteria as they investigated the randomized allocation of beta-blocker therapy in patients with HF and AF (Fig. 1). All these reports were specific AF substudies of the large HF outcome trials (U.S.-Carvedilol [13], CIBIS II [14], MERIT-HF [15], and SENIORS [16]) that compared the effect of beta-blockers with those of placebo. We were

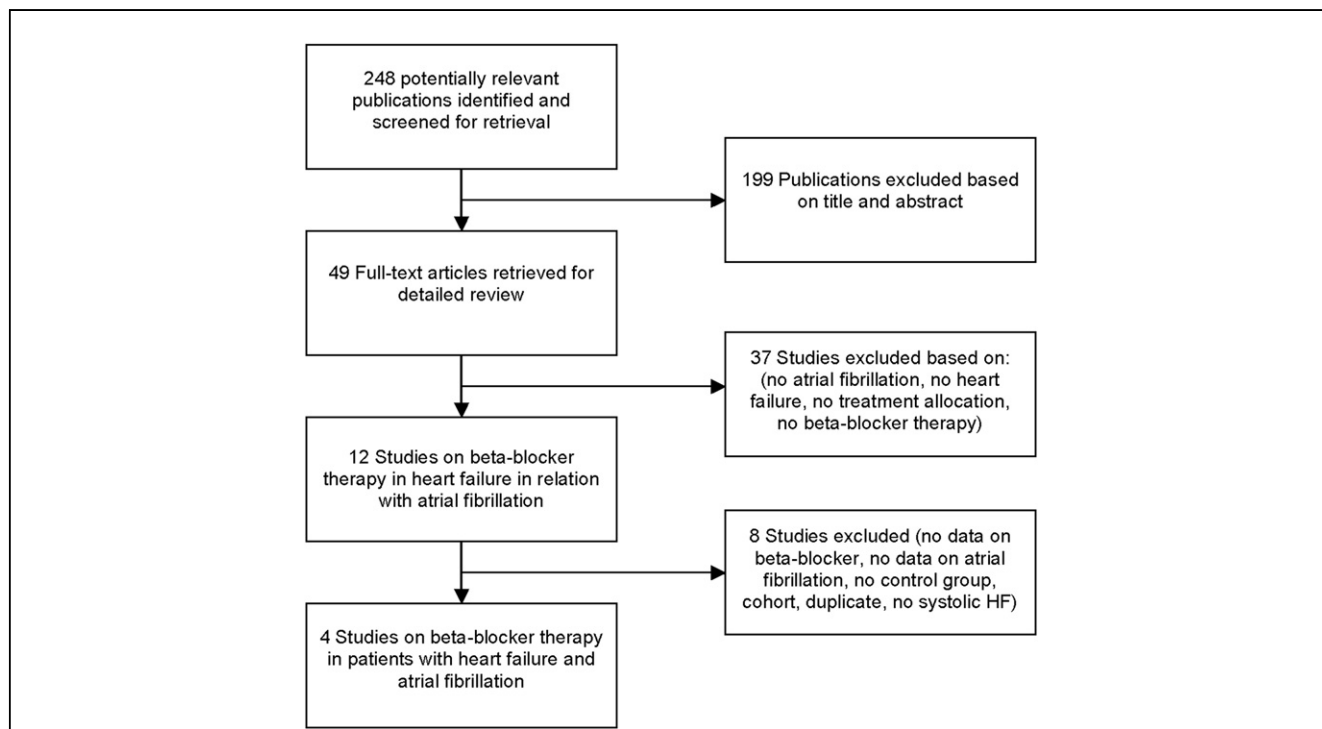


Figure 1. QUORUM Flow Diagram

Quality of reporting of meta-analyses for study selection.

not able to retrieve data from one other large HF beta-blocker study (COPERNICUS), because the presence of AF documented at baseline was not reported (although new onset AF was documented in 1 article) (4). Study quality was scored as “good” for all but one, the U.S.-Carvedilol study, which was scored as “fair.” All 4 studies reported the effect on all-cause mortality, and 3 of the 4 studies also reported HF hospitalizations.

The main characteristics of the studies included in the analysis are reported in Table 1. Overall, 8,680 patients were included. Patient characteristics are shown in Table 2. In total, 1,677 patients (19%) were in AF at baseline (mean age, 68 years of age; 30% women), of whom 842 received a beta-blocker and 835 received placebo. The other 7,003 patients (mean age 63 years; 24% women) had documented sinus rhythm at baseline (3,640 in the beta-blocker group

Table 1. Study Characteristics

First Author Study (Ref. #)	BB	Year	Follow-Up	n (%)	Types of Patients	Endpoints	Major Exclusion Criteria
Joglar <i>et al.</i> U.S.-Carvedilol (13)	Carvedilol	2001	Maximum 400 days	AF: 136 (12%); SR: 958	HF; LVEF ≤35%	All-cause mortality	Unstable HF; heart rate <68 beats/min; Class I or III antiarrhythmic drugs
Lechat <i>et al.</i> CIBIS-II (14)	Bisoprolol	2001	Maximum 800 days	AF: 521 (21%) SR: 2,018	HF; LVEF ≤35%; NYHA III–IV	All-cause mortality; HF hospitalizations	Unstable HF; heart rate <60 beats/min; antiarrhythmic drugs other than amiodarone
Van Veldhuisen <i>et al.</i> MERIT-HF (15)	Metoprolol	2006	Mean F/U 1 yr	AF: 556 (14%); SR: 3,132	HF; LVEF <40%; NYHA II–IV	All-cause mortality; HF; hospitalizations	Unstable HF; heart rate <68 beats/min; CCB or amiodarone
Mulder <i>et al.</i> SENIORS (16)*	Nebivolol	2011	Mean F/U 21 months	AF: 464 (22%); SR: 895	≥70 yrs of age; HF admission <1 yr or LVEF ≤35%	All-cause mortality; HF; hospitalizations	Unstable HF; beta-blocker use

*Only patients from the SENIORS trial with LVEF ≤35% were included.

BB = beta-blocker; CCB = calcium channel blockers; F/U = follow-up; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York heart association; SR = sinus rhythm.

Table 2 Patient Characteristics

First Author (Ref. #)	AF/SR	Age (yrs)	Men (%)	HTN (%)	DM (%)	IHD (%)	Stroke (%)	LVEF (%)	HR (beats/min)	SBP (mm Hg)	Digoxin (%)	ACEi (%)	Diuretics (%)
Joglar et al. (13)	AF	65	90	NA	NA	51	NA	24	87	117	99	96	98
	SR*	58	77	NA	NA	48	NA	25	84	116	91	95	95
Lechat et al. (14)	AF	62	83	17	13	25	12	27	88	131	85	96	98
	SR	61	80	16	13	56	12	28	79	129	43	97	99
Van Veldhuisen et al. (15)	AF	66	62	41	24	34	12	28	84	131	90	91	95
	SR	63	76	44	25	51	8	28	82	130	59	89	90
Mulder et al. (16)	AF	77	63	56	25	35	NA	28	84	136	70	83	92
	SR	76	69	52	28	56	NA	29	77	136	30	79	86

*Sinus rhythm (SR) data were derived from the main study population.

ACEi = angiotensin-converting enzyme inhibitors; DM = history of diabetes; HR = heart rate; HTN = history of hypertension; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NA = not available; SBP = systolic blood pressure.

and 3,363 in the placebo group). Baseline heart rate, change in heart rate, and achieved heart rate in each patient group are shown in Table 3 and Figure 2 (no data were available for the U.S.-Carvedilol study). Heart rate reduction in patients in AF was similar to that in patients in sinus rhythm, although the baseline heart rate was higher in patients with AF. Doses of beta-blockers were similar in CIBIS-II, MERIT-HF, and SENIORS (no data were available for the U.S.-Carvedilol study).

All-cause mortality. Follow-up varied between a maximum of 13 months in the U.S.-Carvedilol study to a mean of 21 months in the SENIORS trial. The crude mortality rates for AF patients receiving beta-blocker therapy and those who were not were 13.5% and 15.7%, respectively, and 8.3% and 13.1%, respectively, for sinus rhythm patients receiving beta-blocker therapy and those who were not. This resulted in a combined mortality risk OR of 0.86 for AF patients (95% CI: 0.66 to 1.13; $p = 0.28$) receiving beta-blocker therapy versus a combined mortality risk OR of 0.63 for sinus rhythm patients (95% CI: 0.54 to 0.73; $p < 0.00001$) receiving beta-blocker therapy (Fig. 3). Interaction analysis showed there was significant interaction on the effect of beta-blocker therapy in AF versus sinus rhythm ($p = 0.048$). There was no heterogeneity observed among the studies with AF included ($I^2 = 0\%$; $p = 0.46$). In metaregression analysis, we found no confounding by any of the variables explored. Figure 4 shows the funnel plot for the main outcome analysis, which shows no evidence of publication bias.

Hospital admission for heart failure. Three of the 4 studies (no data were available for the U.S.-Carvedilol trial) reported the effect of beta-blocker therapy on hospital admission for HF, including 7,586 HF patients (1,541 [20%] AF patients). Beta-blocker therapy in AF patients was not associated with a reduction of HF hospitalizations (16.2% vs. 14.8% events), resulting in an OR of 1.11 (95% CI: 0.85 to 1.47; $p = 0.44$) (Fig. 5). For patients in sinus rhythm (8.5% vs. 14.3% events), beta-blocker therapy was associated with a reduction of HF hospitalizations (OR: 0.58 [0.49 to 0.68]; $p < 0.0001$). Interaction analysis showed a significant interaction on the effect of beta-blocker therapy in AF versus sinus rhythm for HF hospitalizations ($p < 0.001$).

Discussion

The main finding of the present meta-analysis indicates that the effect of beta-blockers in patients with HF and AF is significantly different from the effect of these drugs in patients with HF and sinus rhythm. Indeed, beta-blockers were not found to have a favorable effect on HF hospitalizations or mortality in 1,677 AF patients who had been enrolled in placebo-controlled, randomized studies.

This finding is important as most patients with HF and AF receive beta-blocker treatment. Beta-blockade is recommended in the current guidelines for HF and AF treatment, albeit for different indications (1,23). In HF treatment guidelines, beta-blockers are recommended for all

Table 3 Baseline Heart Rate and Change in Heart Rate

First Author (Ref. #)	Study	Assessment of Baseline HR	Baseline HR (beats/min)	Absolute HR Reduction Beta-Blocker (beats/min)	Relative HR Reduction Beta-Blocker (%)	Beta-Blocker Dose During Study
Joglar et al. (13)	U.S.-Carvedilol	Unclear	AF: 87	AF: -13.0	AF: -14.9	Unclear
			SR: 84*	SR: -12.6*	SR: -15.0*	
Lechat et al. (14)	CIBIS-II	ECG	AF: 88	AF: -8.8	AF: -10.1	Similar in both groups
			SR: 79	SR: -10.6	SR: -13.5	
Van Veldhuisen et al. (15)	MERIT-HF	ECG	AF: 84	AF: -14.8	AF: -17.6	Similar in both groups
			SR: 82	SR: -13.7	SR: -16.7	
Mulder et al. (16)	SENIORS	ECG	AF: 84	AF: -11.0	AF: -13.1	Similar in both groups
			SR: 77	SR: -10.9	SR: -14.2	

*Mean heart rate reduction in the main study population.

AF = atrial fibrillation; HR = heart rate; ECG = electrocardiogram; SR = sinus rhythm.

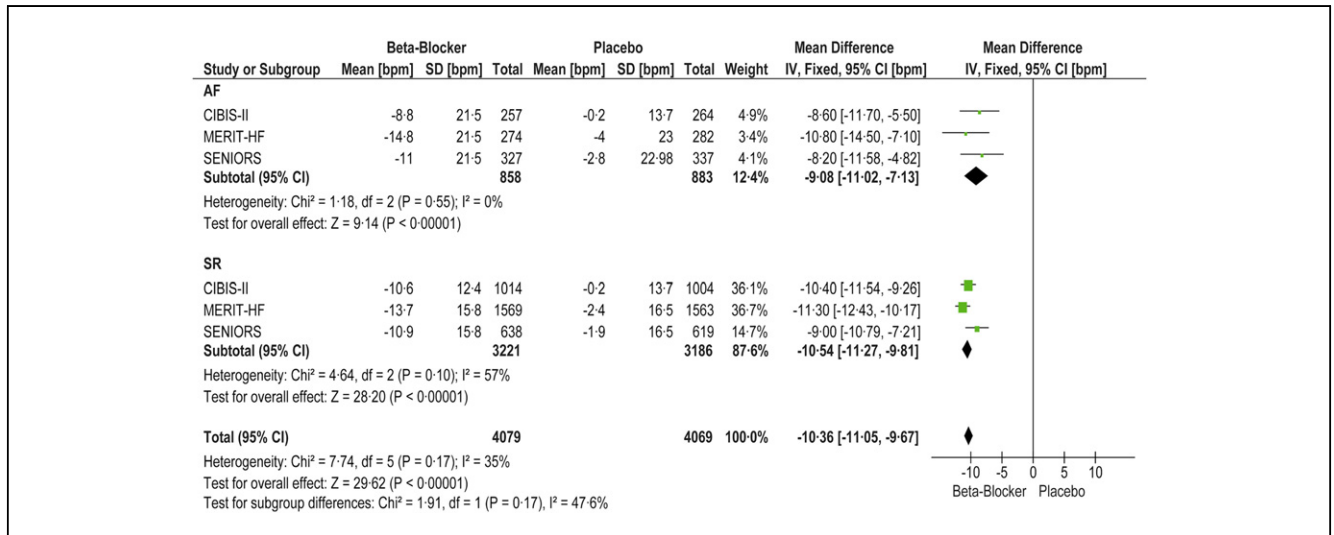


Figure 2 Heart Rate and Heart Rate Reduction

Effect of beta-blocker therapy in patients with heart failure (HF) and atrial fibrillation (AF) and in patients with HF and sinus rhythm.

patients in order to reduce morbidity and mortality, without differentiation regarding rhythm. As such, these drugs are part of the standard medical therapy for all patients with HF and reduced LVEF. In addition, beta-blocker therapy has been shown to prevent new onset or recurrent AF in patients with HF (15,24) after myocardial infarction (25), and also in a relatively low-risk (most hypertension) population (26).

In the AF treatment guidelines, however, beta-blockers are recommended for rate control in order to reduce

AF-related symptoms but not to improve prognosis (23). In line with the guidelines are recent data from the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) program, which showed no predictive value of higher heart rates in HF patients with AF, in contrast to the observations in sinus rhythm patients (11).

How can these different effects of beta-blockers between HF patients with AF and sinus rhythm be explained? First,

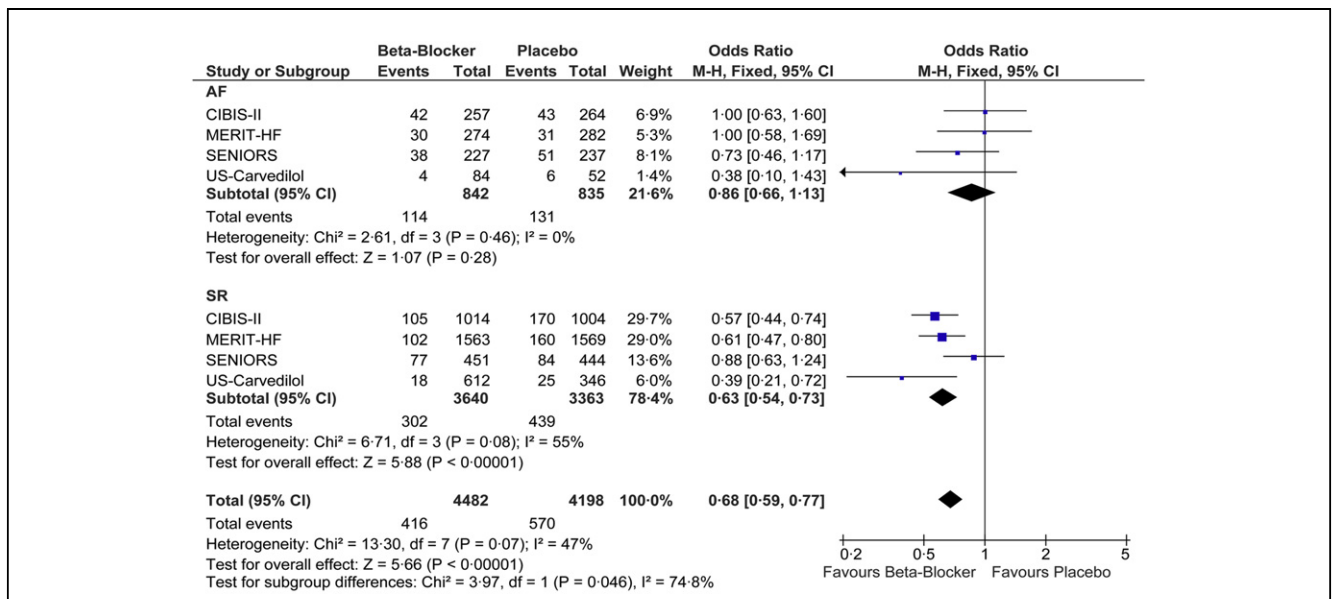


Figure 3 Combined All-Cause Mortality Risk

Effect of beta-blocker therapy in patients with HF and AF and in patients with HF and sinus rhythm. Abbreviations as in Figure 2.

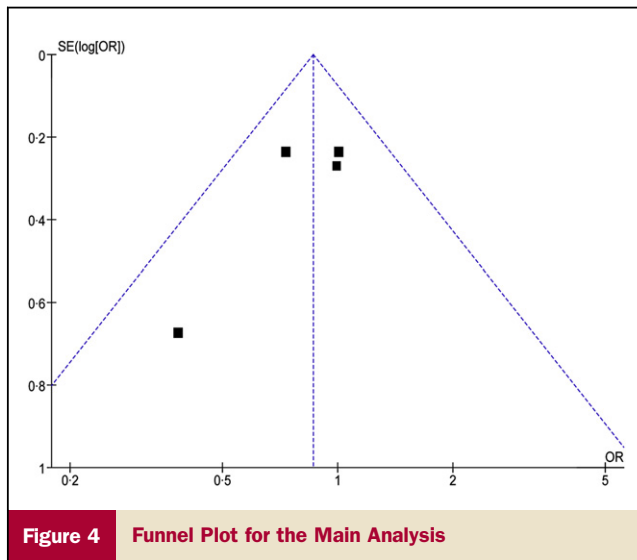


Figure 4 Funnel Plot for the Main Analysis

heart rate reduction by beta-blocker therapy may be less effective in patients with AF than in those with sinus rhythm because the mode of action of beta-blockers is different during AF and sinus rhythm. During sinus rhythm, beta-blockers exert their heart rate lowering effect by targeting the sinus node, whereas during AF their main site of action is the atrioventricular node. In the present analysis, however, we found a similar mean reduction in heart rate for patients with both AF and sinus rhythm with comparable dosages of beta-blockers; however, achieved heart rate was not available and may have been different in AF and sinus rhythm. Second, heart rates were measured only at rest. Heart rate reduction during (moderate) exercise may have

been different between AF and sinus rhythm patients. Indeed, there may be differences in the optimal heart rate at rest and during exercise and optimal heart rate reduction by beta-blockers between both groups of patients. In patients with sinus rhythm, it has been proven that a pronounced reduction in heart rate is associated with improved morbidity and mortality, independent of beta-blocker dose or by additive therapy with selective *I_f*-channel blockade (9,10). For patients with permanent AF, it was recently demonstrated that stricter rate control was not superior to a lenient rate control (12). Third, because of the loss of the atrial kick and irregularity in ventricular response during AF, patients with AF may need a higher heart rate to maintain a similar cardiac output, possibly even more so during HF (27). Fourth, a low heart rate in patients with AF may be an expression of an underlying conduction disorder, which may be associated with impaired outcome itself. Finally, AF in patients with HF may be a marker of a poorer clinical condition leading to a worse outcome, less modifiable by beta-blocker treatment (28).

In addition to these potential explanations, we also cannot exclude the fact that the present findings could apply to some but not all beta-blockers, as differences in pharmacological profiles of beta-blockers may have played a role. Metoprolol and bisoprolol are selective beta-1 receptor antagonists, and carvedilol and nebivolol are beta-blockers with additional vasodilating properties. A subanalysis of the COMET (Carvedilol or Metoprolol European Trial) (including 600 patients with AF) demonstrated that carvedilol had a better effect on outcome than metoprolol (29). The main COMET has been criticized because the dose of the 2 drugs might not have been comparable, as they

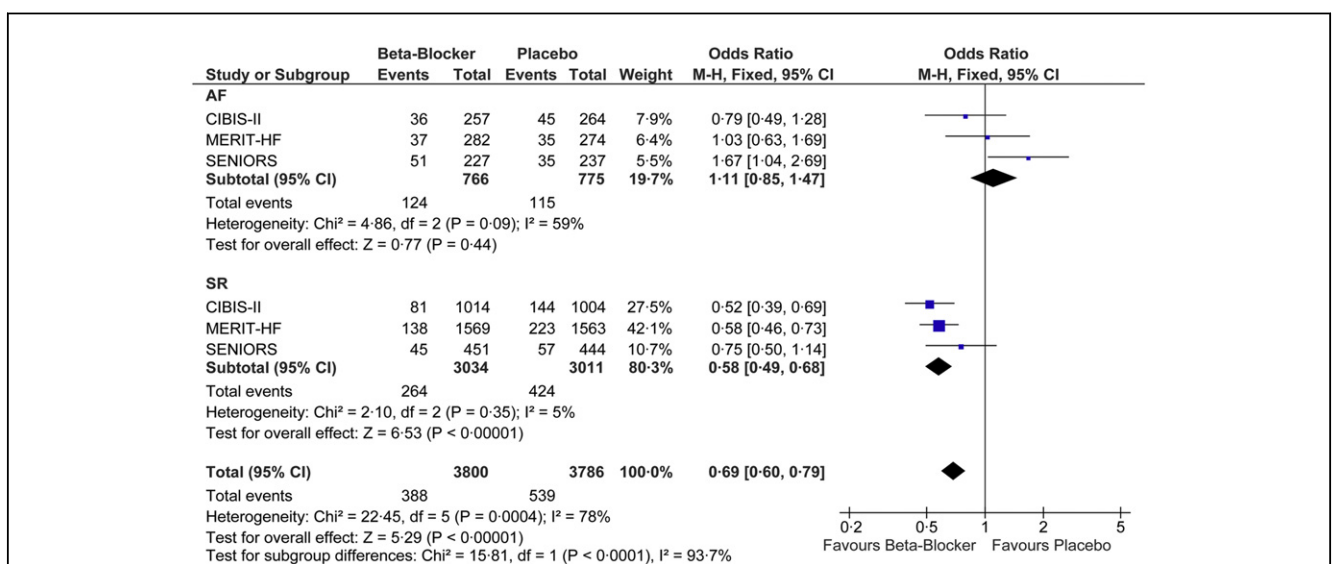


Figure 5 Combined HF Hospitalization Risk

Effect of beta-blocker therapy in patients with HF and AF and in patients with HF and sinus rhythm. Abbreviations as in Figure 2.

lowered heart rate to a different extent. However, given the absence of a relationship between heart rate lowering and outcome in AF patients, this criticism may be less relevant in this subpopulation of AF patients. It must be noted that carvedilol had a relatively favorable effect in the present analysis in the AF patients in the U.S.-Carvedilol study (13), but these patients had milder disease than in the other studies, which also may have affected the results.

Beta-blockers are standard therapy for HF. Other drugs that are generally recommended for HF are angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers (or mineralocorticoid antagonists). It is remarkable that all these classes of drugs have been shown to be at least as effective in patients with AF as they are in patients with sinus rhythm in analyses similar to the present study (28,30).

Study limitations. We conducted a meta-analysis of non-pre-specified subgroups of large randomized trials, and this analysis has some limitations that merit consideration. Although the number of AF patients in the included randomized studies was 1,677 with 145 events, this is still low for survival analysis, and we cannot exclude the possibility that lack of power may have played a role. On the other hand, when ORs of beta-blocker therapy in AF patients were similar to those in sinus rhythm patients, there would have been sufficient power to detect an effect as large as found in sinus rhythm patients. However, if the effect of beta-blocker therapy is attenuated in AF, larger sample sizes are needed to draw definite conclusions. Nevertheless, there was a significant interaction with regard to this (beta-blocker) treatment effect between AF and sinus rhythm patients, which further supports our findings. Also, in the present analysis, we pooled the effects of different beta-blocker therapies and thereby assumed a class effect. However, specific differences in pharmacologic profiles may have added to the heterogeneity of our cohort and thereby the results. Inherent limitations of pooled analysis of studies include the limited availability of confounding variables, including history of AF, duration of AF, pattern of AF (paroxysmal vs persistent and/or permanent AF), new onset AF, dose response, and tolerance to the drugs. In metaregression analysis, we explored possible study characteristics that might have influenced the pooled estimates. However, given the small number of studies included, we had only limited power to find significant confounders. Finally, this analysis pooled study group estimates and did not assess individual patient data, which limits the possibility of adjustment for individual patient characteristics.

Conclusions

The present analysis suggests that the effect of beta-blockade in HF patients with AF with regard to outcome is less than in HF patients with sinus rhythm. Clearly, prospective randomized controlled trials in HF specifically aiming at AF

patients are warranted to study the prognostic effects of beta-blockers in this population.

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